Prognostic factors in glioblastoma multiforme patients receiving high-dose particle radiotherapy or conventional radiotherapy

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ABSTRACT. The aim of this study was to evaluate the influence of prognostic factors related to patient selection on survival outcomes. Survival outcomes were retrospectively analysed in a consecutive series of 67 newly diagnosed glioblastoma multiforme (GBM) patients who had received either conventional fractionated photon radiotherapy (CRT) or high-dose particle radiotherapy (HDT). In the CRT protocol, a total dose of 60.0–61.2 Gy was administered. In the HDT protocol, an average dose of approximately 30 GyE in a single session and additional fractionated photon irradiation of total dose 30 Gy were administered to patients receiving boron neutron capture therapy; and a total dose of 96.6 GyE was administered to patients receiving proton therapy. Most of the patients had received chemotherapy with nimustine hydrochloride (ACNU) alone or with ACNU, procarbazine and vincristine. The median overall survival (OS) and progression-free survival times for all patients were 17.7 months [95% confidence interval (CI), 14.6–20.9 months] and 7.8 months (95% CI, 5.7–9.9 months), respectively. The 1- and 2-year survival rates were 67.2% and 33.7%, respectively. For patients treated with HDT, the median OS was 24.4 months (95% CI, 18.2–30.5 months), compared with 14.2 months (95% CI, 10.0–18.3 months) for those treated with CRT. The Cox proportional hazards model revealed radiation modality (HDT vs CRT) and European Organisation for Research and Treatment of Cancer recursive partitioning analysis class to be the significant prognostic factors. Age, sex, pre-operative performance status, treatment with or without advanced neuroimaging, extent of surgery and regimen of chemotherapy were not statistically significant factors in predicting prognosis. The median OS was 18.5 months (95% CI, 9.9–27.1 months) in patients of 65 years and older, compared with 16.8 months (95% CI, 13.6–20.1 months) in those 64 years and younger ($p=0.871$). The positive effect of HDT treatment is unlikely to reflect patient selection alone. Randomised trials with strictly controlled inclusion criteria to ensure the comparable selection of patients are required to demonstrate conclusively that prolonged survival can be attributed to high-dose particle radiotherapies.

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Glioblastoma multiforme (GBM) is a highly infiltrative primary malignant brain tumour in adults. The prognosis of GBM is generally extremely poor, and there has been little improvement in survival rates over the past three decades [1, 2]. Several randomised trials have demonstrated the survival benefits of conventional fractionated photon radiotherapy at a total dose of 45–60 Gy; the median overall survival (OS) time (in these trials was 5.8–15.5 months [3–7]. Currently, conventional fractionated photon radiotherapy of approximately 60 Gy with concomitant and adjuvant use of temozolomide is recognised as the standard post-operative treatment for newly diagnosed GBM [8, 9]. However, the 5-year survival rate with this standard therapy is <10% [9], suggesting that alternative therapeutic strategies are desperately needed.

Most dose escalation studies for radiotherapy have been designed as case series of a small number of

selected patients who underwent additional stereotactic radiosurgery, fractionated proton beam radiation, intensity-modulated radiotherapy or another type of conformal radiotherapy [10–12]. Studies showing the better outcomes (median OS range, 9.5–25 months) suggested that a radiation dose of at least 90 Gy of hyperfractionated radiotherapy should be used for irradiation in order to accomplish local tumour control. There has, however, been no randomised controlled trial to provide evidence in support of these studies, nor has there been any trial using any form of high-dose radiotherapy that warrants a follow-up study [10, 13]. Thus, controversy remains regarding both the efficacy of high-dose radiotherapy and the influence of strict patient selection on the outcomes achieved with this type of treatment. The high-dose irradiation of a small-volume target could minimise central recurrence and any adverse events that are dependent on radiation dose in such trials. However, recurrences often occur in target volumes that receive a relatively low-dose treatment. The 5-year survival rate with conventional-dose radiotherapy alone is reported at

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approximately 1% [9], suggesting that this treatment has limited success in most patients.

We recently reported the use of two different types of high-dose particle radiotherapy, boron neutron capture therapy (BNCT) and proton therapy (PT), in glioblastoma [14, 15]. These radiotherapies for newly diagnosed GBM were administered on the basis of different selection criteria. Both showed an acceptable OS (*i.e.* 25.7 months in the BNCT group and 21.6 months in PT group), with acceptable adverse events [14, 15]. Several different factors [*e.g.* age, pre-operative performance status (PS), tumour location, extent of surgery and use of conventional radiotherapy] have previously been shown to be prognostic of survival in patients with GBM [16–20]. Here, we aim to evaluate the influence of such patient selection-related factors on survival. Survival outcomes and prognostic factors were retrospectively analysed using our institutional consecutive series of newly diagnosed GBM patients who had received either conventional fractionated photon radiotherapy (CRT) or high-dose particle radiotherapy (HDT). We report the combined updated results for all patients treated by either form of particle therapy.

Materials and methods

We investigated 67 consecutive patients with newly diagnosed supratentorial GBM (Grade IV) who were treated at Tsukuba University Hospital, Japan, between January 1998 and August 2007. The patients were histopathologically diagnosed according to the classification system of the World Health Organization (WHO). Some of the survival data for patients who received PT or BNCT have been reported in earlier publications where they were assessed after different follow-up periods and using different survival analysis determinations [14, 15].

Maximal safe resection was intended to remove all gadolinium-enhanced masses observed by MRI, *i.e.* the non-eloquent brain tissue surrounding a mass was targeted for removal with the aim of preserving neurological function in unresected areas of eloquent brain tissue. To this end, 5-aminolevulinic-acid-induced fluorescence guidance, neuronavigation and intraoperative monitoring were incorporated into the treatment. The navigation-guided fence-post procedure was carried out as previously reported [21] to treat the non-eloquent portions of tumours. In cases involving tumours that were located close to areas of eloquent tissue, we inserted silicon tubes along the boundary between the eloquent and non-eloquent tissue, as guided by MRI. The phrase “advanced neuro-imaging” is used to refer to all surgical interventions involving fluorescence guidance and/or neuronavigation.

The post-operative radiation schedule for patients with GBM at our facilities consisted of three protocols. As the standard radiotherapy, daily CRT (1.8–2.0 Gy) was administered five times per week, amounting to a total overall dose of 60.0–61.2 Gy. For selected patients, HDT, consisting of either BNCT or PT, was used. In the BNCT protocol, the gross tumor volume (GTV) and the clinical target volume (CTV)-1 were defined as the residual gadolinium-enhancing volume. CTV-2 and CTV-3 were defined as GTV plus a margin of 2 or 3 cm, respectively. An average dose of

approximately 30 GyE in a single session and additional fractionated photon irradiation totalling 30 Gy were administered to the GTV. The detailed protocol for BNCT has been described elsewhere [14]. BNCT was administered to patients with a supratentorial unilateral tumour, located at no deeper than 7 cm from the brain surface, who had a Karnofsky performance status (KPS) of ≥ 50 . In the PT protocol, CTV-1 was defined as in the BNCT protocol. However, CTV-2 was defined as GTV plus a margin of 1 cm, and CTV-3 was defined to include the surrounding oedema. Furthermore, in the PT protocol, a planning target volume (PTV) adopted was defined as the corresponding CTV plus a margin of 5 mm to allow for set-up error. Conventional photon radiotherapy (50.4 Gy in 28 fractions) was delivered to PTV-3 in the morning. In the first half of the protocol, additional concomitant boost proton radiotherapy (23.1 GyE in 14 fractions) was delivered to PTV-2 >6 h after this photon radiotherapy. Subsequently, in the latter half of the protocol, proton radiotherapy (23.1 GyE in 14 fractions) was delivered to PTV-1. As a result, the total dose was 96.6 GyE in 56 fractions for PTV-1, 73.5 GyE in 42 fractions for PTV-2 and 50.4 Gy in 28 fractions for PTV-3 [15].

The following criteria were used to select patients for PT: the presence of a supratentorial tumour lacking involvement of the brain stem or thalamus, a maximum post-operative tumour diameter of <4 cm, and a KPS of ≥ 60 . BNCT was administered to 15 patients and PT to 17 patients. The combination therapy (PAV), consisting of procarbazine, nimustine hydrochloride (ACNU) and vincristine, was administered as the standard concomitant chemotherapy in combination with CRT. For patients at high risk of adverse events with PAV therapy (*i.e.* elderly patients or patients in poor neurological or general condition), ACNU alone was typically used as the concomitant chemotherapy. ACNU was also used in combination with HDT.

Statistical analysis

Statistical analysis was performed using SPSS software (version 11.0.1J; SPSS Inc., Chicago, IL; now an IBM company). OS and progression-free survival (PFS) were used to investigate the prognostic impact of the analysed variables. OS was defined as the time lapse from surgery until death or the final follow-up. PFS time was defined as the time lapse from surgery until the detection of progression or the final follow-up. Survival probabilities were calculated using the Kaplan–Meier method, and differences among patient groups were evaluated using the log-rank test. The Cox proportional hazards model was used to test the following prognostic factors in univariate and multivariate analyses: age (<65 *vs* ≥ 65 years), sex (female *vs* male), pre-operative PS (0–2 *vs* 3–4), European Organisation for Research and Treatment of Cancer (EORTC) recursive partitioning analysis (RPA) Class (III–IV *vs* V) [22], advanced neuro-imaging (with *vs* without), extent of surgery (complete resection *vs* other), chemotherapy (ACNU *vs* other) and radiation modality (HDT *vs* CRT).

Factors with a probability value of <0.05 on univariate analysis were selected for testing in the multivariate analysis. The results are expressed with relative risk and a 95% confidence interval (CI).

Table 1. Characteristics of 67 patients with glioblastoma multiforme

Characteristics	Number of patients (%)
Age	
Median 59.0 years	
Range 31–84 years	
Sex	
Male	34 (51%)
Female	33 (49%)
Side	
Left	33 (49%)
Right	27 (40%)
Midline or bilateral	7 (10%)
Location	
Frontal lobe	32 (48%)
Temporal lobe	19 (28%)
Parietal lobe	17 (25%)
Occipital lobe	1 (1%)
Other	6 (9%)
Advanced neuro-imaging ^a	
Yes	31 (46%)
No	36 (54%)
Extent of surgery	
Complete	13 (19%)
Partial	47 (70%)
Biopsy	7 (10%)
Chemotherapy	
Nimustine hydrochloride	45 (67%)
Other	2 (3%)
None	20 (30%)
Radiotherapy	
High dose	32 (48%)
Conventional dose	35 (52%)
WHO performance status	
0	6 (9%)
1	30 (45%)
2	12 (18%)
3	10 (15%)
4	9 (13%)
EORTC-RPA class ^b	
III	9 (13%)
IV	21 (31%)
V	37 (55%)

EDRTC, European Organisation for Research and Treatment of Cancer; RPA, recursive partitioning analysis; WHO, World Health Organization.

^aAdvanced neuro-imaging indicates the use of 5-aminolevulinic-acid-induced fluorescence guidance and/or neuro-navigation.

^bRadiation Therapy Oncology Group RPA Class VI patients were included in EORTC-RPA Class V.

Results

The characteristics of the 67 patients are summarised in Table 1. A total of 34 men and 33 women, aged 31–84 years (median, 59 years), were included in the analysis. Surgical resection resulted in complete resection of the tumour in 13 patients (19%), in partial resection in 47 patients (70%) and biopsy in 7 patients (10%). 47 patients (70%) received chemotherapy with ACNU or other agents. 32 patients (48%) received HDT and 35 (52%) received CRT; consequently, all 67 patients received 1 of the 2 types of radiotherapy. There were 6 patients (9%) with a WHO PS of 0, 30 (45%) with a PS of 1, 12 (18%) with a PS of 2, 10 (15%) with a PS of 3 and 9 (13%) with a PS of 4. 9 patients (13%) were categorised as having the best GBM prognosis (Class III), whereas 21 (31%) were in Class IV and 37 (55%) in Class V, according to the EORTC-RPA classification system.

Nine patients were alive at the time of analysis, with a mean follow-up time of 21.4 (range, 1.0–71.2) months. The median OS for all patients was 17.7 (95% CI, 14.6–20.9) months. The 1- and 2-year survival rates were 67.2% and 33.7%, respectively. The median PFS time in this series was 7.8 (95% CI, 5.7–9.9) months. The 1- and 2-year PFS rates were 32.6 and 18.4%, respectively.

The univariate and multivariate analyses of the prognostic factors examined in this study are shown in Tables 2 and 3, respectively. The multivariate analysis revealed that radiation modality and EORTC-RPA class were significant prognostic factors. The median OS was 24.4 (95% CI, 18.2–30.5) months for patients treated with HDT, compared with 14.2 (95% CI, 10.0–18.3) months for those treated with CRT (Figure 1). Other previously reported prognostic factors, such as age, sex, pre-operative PS, treatment with or without advanced neuro-imaging, extent of surgery and chemotherapy regimen, were not statistically significant according to the multivariate analysis. The median OS was 18.5 (95% CI, 9.9–27.1) months in patients 65 years and older, compared with 16.8 (95% CI, 13.6–20.1) months in those aged 64 years and younger ($p=0.871$).

Patients who were treated with HDT had a significantly better pre-operative PS than patients treated with CRT ($p=0.025$). Similarly, patients who were treated with HDT were more likely to have undergone complete resection than those treated with CRT (28.1% compared with 11.4%, respectively; $p=0.078$) and were more likely to be categorised in the better prognostic group (III–IV compared with V; $p=0.059$), but neither of these differences was statistically significant. Other clinical characteristics,

Table 2. Univariate analysis of prognostic factors for the survival of patients with glioblastoma multiforme

Variable	Hazard ratio (95% CI)	p-value
Age (<65 vs ≥65 years)	0.954 (0.539–1.687)	0.871
Sex (female vs male)	0.600 (0.351–1.023)	0.061
WHO performance status (0–2 vs 3–4)	0.525 (0.295–0.936)	0.029
EORTC-RPA Class (III–IV vs V)	0.502 (0.289–0.872)	0.014
Advanced neuro-imaging (with vs without)	0.731 (0.430–1.244)	0.248
Extent of resection (complete vs others)	0.735 (0.379–1.424)	0.361
Chemotherapy (ACNU vs others)	0.632 (0.365–1.091)	0.100
Radiotherapy (high dose vs conventional dose)	0.443 (0.258–0.762)	0.003

ACNU, nimustine hydrochloride; CI, confidence interval; EORTC-RPA, European Organisation for Research and Treatment of Cancer recursive partitioning analysis; WHO, World Health Organization.

Table 3. Multivariate analysis of prognostic factors for the survival of patients with glioblastoma multiforme

Variable	Hazard ratio (95% CI)	p-value
WHO performance status (0–2 vs 3–4)	0.634 (0.352–1.142)	0.129
EORTC-RPA Class (III–IV vs V)	0.544 (0.310–0.954)	0.034
Radiotherapy (high dose vs conventional dose)	0.495 (0.284–0.862)	0.013

CI, confidence interval; EORTC-RPA, European Organisation for Research and Treatment of Cancer recursive partitioning analysis; WHO, World Health Organization.

i.e. age, sex, advanced neuro-imaging and chemotherapy regimen, did not differ between patients who underwent HDT and those treated with CRT (Table 4).

Discussion

The median OS for all patients was 17.7 months; a longer median OS of 24.4 months was seen in the HDT group, whereas the CRT group had an OS of 14.2 months. Receiving either HDT or CRT was also independently significant in determining prognosis. The survival data for the CRT patients in this study were comparable with those

of reported previously for patients treated with the standard therapies. Patient selection (*e.g.* age, PS etc.) for the HDT group appeared not to be a major factor influencing survival time, nor did it negatively influence the survival time of the CRT patients.

It is generally accepted that the concomitant and adjuvant use of temozolomide with conventional fractionated photon radiotherapy can be effective in treating post-operative GBM with minimal additional toxicity, and a significant survival advantage has been demonstrated for this approach compared with the administration of radiotherapy alone. The median OS in a randomised controlled trial by Stupp et al [8] was 14.6 months with

Figure 1. Kaplan–Meier estimates of overall survival according to radiation modality. The hazard ratio for death among patients treated with high-dose radiotherapy, as compared with that among patients treated with conventional fractionated photon radiotherapy, was 0.44 (95% confidence interval, 0.26–0.76; $p < 0.01$).

Table 4. Clinical characteristics of patients treated with high-dose particle radiotherapy compared with those who underwent conventional fractionated photon radiotherapy

Characteristics	Number of patients (%)		p-value
	High dose	Conventional dose	
Age			
<65 years	24	22	0.210
≥65 years	8	13	
Sex			
Male	14	20	0.198
Female	18	15	
Advanced neuro-imaging			
Yes	14	17	0.441
No	18	18	
Extent of surgery			
Complete resection	9	4	0.078
Other	23	31	
Chemotherapy			
ACNU	21	24	0.501
Other	11	11	
WHO performance status			
0–2	27	21	0.025
3–4	5	14	
EORTC-RPA Class			
III–IV	18	12	0.059
V	14	23	

ACNU, nimustine hydrochloride; EORTC-RPA, European Organisation for Research and Treatment of Cancer recursive partitioning analysis; WHO, World Health Organization.

temozolomide plus radiotherapy, and 12.1 months with radiotherapy alone. The median OS of CRT patients observed in our study was comparable with that of patients in the temozolomide treatment group of Stupp et al's study, whereas the median OS of all patients in our study was longer. The patient characteristic data from the report by Stupp et al showed that patients in their temozolomide treatment group tended to be younger, to have better PS (0–1), and to belong to less high-risk (EORTC-RPA Class V) populations (Table 5). These findings suggest that the favourable survival data from all patients and from those who underwent HDT in this study were unlikely to reflect patient selection alone. However, the more extensive surgery (39% of patients in the EORTC-National Cancer Institute of Canada Clinical Trials Group (NCIC) study underwent complete resection [9] *vs* 19% in our study), more-moderate risk populations (53% of patients in the EORTC-NCIC study were EORTC-RPA Class IV [9] *vs* 31% in our study), aggressive salvage treatment and other indeterminate factors, such as surgical technique and administration of standard care, may have positively influenced the survival data in the EORTC-NCIC study. Additionally, small sample size and inconsistent and non-controlled patient characteristics may have affected our results and thus pose limitations on the findings of the present study.

In this study, the median OS of GBM patients increased from 15.2 (95% CI, 8.1–22.3) months for patients first treated between 1982 and 1997 to 17.7 (95% CI, 14.6–20.9) months for those first treated between 1998 and 2007, although this trend was not statistically significant ($p=0.086$). The 2-year relative survival rate also increased from 23.6% between for patients first treated 1982 and 1997 to 33.7% for those first treated between 1998 and 2007. Advances in surgical techniques, such as the introduction of fluorescence guidance in 1999

Table 5. Comparison of patient characteristics in the conventional fractionated photon radiotherapy plus continuous daily temozolomide (CRT+TMZ) group of the European Organisation for Research and Treatment of Cancer National Cancer Institute of Canada Clinical Trials Group study [9] patients and all patients in our study

Characteristics	CRT+TMZ	This study
Number of patients	287	67
Age		
Median	56 years	59 years
Range	19–70 years	31–84 years
Sex		
Male	185 (64%)	34 (51%)
Female	102 (36%)	33 (49%)
Extent of surgery		
Complete	113 (39%)	13 (19%)
Partial	126 (44%)	47 (70%)
Biopsy	48 (17%)	7 (10%)
WHO performance status		
0	113 (39%)	6 (9%)
1	136 (47%)	30 (45%)
2	38 (13%)	12 (18%)
3	0 (0%)	10 (15%)
4	0 (0%)	9 (13%)
EORTC-RPA class		
III	42 (15%)	9 (13%)
IV	152 (53%)	21 (31%)
V	93 (32%)	37 (55%)
Number of progressing tumours	244 (85%)	59 (88%)
Salvage surgery	66 ^a (27%)	20 (34%)
Salvage chemotherapy	142 ^a (58%)	54 (92%)

EORTC-RPA, European Organisation for Research and Treatment of Cancer recursive partitioning analysis; WHO, World Health Organization.

^aCalculated by the present authors.

and of neuro-navigation in 2005, have been implemented at our institute alongside improvements in chemotherapeutic agents; however, no significant differences in the extent of surgery or chemotherapy regimen were observed between the two time periods (*i.e.* pre- and post-1998). There remains no reliable evidence that these new surgical approaches or chemotherapy regimen are having a positive effect on OS. It is possible, therefore, that the improvements in OS may not have been related to surgical approach but rather to changes made to the BNCT protocol (since 1998) and to the PT protocol (since 2001), when rotating gantries and regular daily fractionation became possible.

In the BNCT patient series, we observed some acute toxicities, such as mild erythema (commonly observed) and transient orbital swelling (observed in one patient; 6.7%), but no late toxicity was observed during the follow-up periods. In the PT patient series, acute toxicities such as radiation dermatitis (commonly observed), rash (observed in one patient; 5.9%) and headache (in five patients; 29.4%) were observed. As for late toxicity, radiation necrosis and leukoencephalopathy were each observed in one patient (5.9%) [14, 15]. These data indicate that toxicity seems to be at an acceptable level for our HDT protocol, but incidence of late toxicities, such as radiation necrosis and leukoencephalopathy, in survivors needs to be monitored and clarified after a longer follow-up period.

Patient age has been reported to be a strong prognostic factor in the treatment of GBM. In the RPA of EORTC, being 50 years old or older is a significant prognostic factor in the categorisation of disease. In the present study, however, no correlation has been found between age and prognosis. Recently, there has been a significant improvement in the survival of elderly patients with GBM, thanks to the introduction of aggressive treatments [23–25]. In the present series, no statistically significant difference was observed in age-related survival probability. The mean age of PT and BNCT patients was 57 and 60 years, respectively. Aggressive treatment of elderly patients with GBM at our institute appears to have minimised any age-related difference in survival probability.

Patients who were treated with HDT had a better pre-operative PS and were more likely to have undergone complete resection than patients treated with CRT. It was not possible to separate the effects of HDT from the selection bias towards patients with a better prognosis, because the inclusion criteria for our HDT modalities, which are based on the characteristics of GBM patients, involve the restriction of PS and limitations to tumour size and location, both of which are correlated with the difficulty of resection. Even in patients categorised in the worst prognostic group (EORTC-RPA Class V), however, OS was significantly prolonged for those who had received HDT compared with those treated with CRT ($p=0.007$). Similarly, among patients who underwent partial resection or biopsy, the OS was also significantly prolonged for those who received HDT *vs* those treated with CRT ($p=0.005$). These results indicate that the survival benefits of HDT are unlikely to reflect patient selection alone.

Conclusions

It is generally accepted that both the size and the location of a tumour, as well as patient performance

status, should be considered when evaluating the safety and efficacy of high-dose particle radiotherapies. In this study, patients selected to receive HDT showed longer survival times than those treated with CRT. Although HDT, compared with CRT, was factored out as a significant favourable prognostic factor, other major prognostic factors did not appear to be confounding. The results of this study suggest that the positive effects of HDT on patient survival are unlikely to reflect patient selection alone. Randomised trials with strictly controlled inclusion criteria to enforce the comparable selection of patients are required to demonstrate conclusively that prolonged survival is a result of these high-dose radiotherapies.

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